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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,840	02/15/2002	Andrew J. Murphy	REG 780D	2776

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Linda O. Palladino
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,840	MURPHY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/6/05 has been entered.

Applicants' amendment, filed 9/6/05, has been entered. Claims 1-78 are cancelled. Claims 79-94 are added and under current examination.

Specification

The objection to the disclosure for containing an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of Applicants' amendment to the specification.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
There is no date next to the signature of George D. Yancopoulous.

Double Patenting

Applicants' Terminal Disclaimer, field 6/29/05, is proper and has been entered over U.S. Patent No. 6,586,251 B2 and Patent No. 6,596,541 B2.

Claim Rejections - 35 USC § 112

The prior rejection of claims 51-58, 60, 63-71 and 75-76 under 35 U.S.C> 112, first paragraph, for enablement, is withdrawn in view of Applicants' amendment to the claims. A new rejection appears below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 79-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for creating a modified endogenous gene locus in a mouse ES cells, wherein the LTVEC is produced using *bacterial homologous recombination*, and introducing the LTVEC into an isolated mouse ES cell, and using a quantitative assay in order to detect the reduce copy number of the unmodified allele compared to that of a reference gene in the cell to indicate the modification of allele, the specification does not reasonably provide enablement for the claimed methods, which do not specifically recite using bacterial homologous recombination. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or us the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention/Breadth of the claims. The claims are directed to methods of creating, in isolated mouse ES cells, a modified endogenous gene locus by providing a large targeting vector for use in eukaryotic cells (LTVEC) comprising

a site specific-recombination site, a downstream homology arm containing a region homologous to a 3' end of the endogenous gene locus region and an upstream homology arm within the locus, wherein the homology arms are greater than 20 kb and the site-specific recombination site is selected from loxP lox511, lox2272, introducing the LTVEC into an isolated mouse ES cell and using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele (MOA) in the endogenous gene locus of the cell, wherein the endogenous gene locus is flanked by the site-specific recombination site. Specific embodiments of the claims are directed to particular quantitative assays that would be used to detect the reduced copy number of the MOA.

Guidance of the Specification/The Existence of Working Examples. The specification teaches utilizing targeting vectors with larger homology arms than that which is available in the art, where these vectors have large genomic inserts. These vectors can produce larger modifications in resultant transgenic animals, and the long regions of homology could increase the targeting frequency of "hard to target" loci in eukaryotic cells, particularly because the targeting of homologous recombination appears to be directly related to the total homology contained within the targeting vector. See p. 3, lines 6-21. Particularly, the specification teaches that modification into large genomic fragments have been largely solved through the use of homologous recombination in bacteria, and that this allows for the construction of vectors that contain very large regions of homology to eukaryotic endogenous genes or chromosomal loci. The specification teaches that once these vectors have been made, the difficulty lies in detecting the rare targeting events when the homology arms are larger than 10-20kb. See p. 3, lines 23-34. Thus, the instant invention is directed to using bacterial homologous recombination in order to engineer a desired genetic modification within a large, cloned genomic fragment, to produce a LTVEC, the introduction of the LTVEC into a eukaryotic cell to modify

the endogenous chromosomal locus of interest, and the analysis of the result cells to identify positive clones wherein the targeted allele has been modified. See p. 4, lines 23-32.

The working examples of the specification teaches the selection of a large genomic DNA clone containing the mouse OCR10 gene and the generation of an LTVEC from this BAC. The LTVEC was then used to delete a portion of the endogenous mouse OCR10 gene, and replacing the initiation codon of OCR10 and inserting a selectable marker (LacZ) in the resultant cells. See Example 1. The specification teaches that bacterial homologous recombination was employed in order to precisely replace the mOCR10 coding region with the insertion cassette (see p. 36, lines 5-11). This resulted in the an approximate 20 kb deletion in the mOCR10 locus, while leaving approximately 130 kb of upstream homology and 32 kb of downstream homology. See p. 36, lines 11-16. ES cells were transfected with this LTVEC and the targeting efficiency was analyzed (see Table 1).

State of the Art/Predictability of the Art. The specification teaches that the instantly disclosed vectors provide a means to introduce large DNA fragments by homologous recombination, into endogenous DNA sequences, and then quickly identify positive clones. The specification states that various factors have been problematic in generating these vectors. For example, the specification teaches that the engineering of precise genetic modifications into very large genomic fragments has been solved through the use of homologous recombination in bacteria (see p. 3, lines 23-25) and that there is difficulty in identifying the resultant transformants (p. 3, lines 30-35). The state of the art supports that bacterial recombination and BACs are often used in order to allow the cloning of large fragments of DNA. For example, Hong *et al.* (**Analytical Biochem.**, 291: 142-148 (2001)) state that, "[T]here is an increased need for special vector systems that allow cloning of large fragments of DNA and subsequent regulated expressions of the fragments in target cells." See p. 142, col. 1-2, bridging ¶. They state that BACs are systems that are useful for

cloning these large fragments of DNA (see p. 142, 2nd column). The instant specification is directed to using bacterial recombination in order to produce the claimed LTVECs. Giraldo *et al.* (**Transgenic Res.**, 10 :83-103 (2001)) review the state of the art of producing transgenic animals using artificial chromosomes, and particularly BACs. They teach that BACs overcome the unpredictibilities associated with using YACS, such as insert chimaerism, insert instability, rearrangement and potential contamination with endogenous yeast chromosomes (see p. 91, 2nd column, 1st paragraph). They particularly teach that BACs are able to stably propagate large DNA inserts, and show low frequency of chimaerism and higher stability (see p. 92, 1st column, 2nd paragraph).

The Amount of Experimentation Necessary. The working examples in the specification show that in order to produce the LTVEC, a BAC would be required that would have the large fragments of DNA that would be used to homologously recombine with the endogenous sequence. However, the claims do not limit the invention to require either BAC (or using bacterial homologous recombination) to produce the LTVEC. Accordingly, in view of the state of the art, which shows that bacterial recombination would be necessary in order to produce the LTVEC, which would then be used in the methods of modification an endogenous gene locus in an isolated mouse ES cells, the lack of teaching or guidance provided by the specification with regard to practicing the claimed method without using bacterial homologous recombination, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 79-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 79-81, 88-90 and 94 are unclear. The preamble of the claims relate to a method of creating a modified gene locus in an isolated mouse ES cell. However, the steps of the method do not refer to an isolated mouse ES cell, but an isolated cell. See step (b) of claim 79, for example. Thus, the method steps fail to relate back to the preamble. Appropriate correction is required. Claims 82-87 depend from claim 81; claims 91-93 depend from claim 90.

Claim 87 contains the trademark/trade name Taqman®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe Taqman® and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

The prior rejection of claims 51-55, 57-60, 63, 65-69, 71, 75 and 76 under 35 U.S.C. 102(b) as being anticipated by Kuncherlapati *et al.* (cited previously)is withdrawn in view of Applicants' arguments. In particular, the cited art does not describe large DNA vectors that have homology arms that are greater than 20 kb which is required by the claims.

Claim Rejections - 35 USC § 103

The prior rejection of claims 51-58, 60, 63, 65-71 and 75-76 under 35 U.S.C. 103(a) as being unpatentable over Kuncherlapati *et al.* when taken with Yang *et al.*; and the rejection of claims 51-55, 57-58, 60, 63-69, 71, 75-78 under 35 U.S.C. 103(a) as being unpatentable over Kuncherlapati *et al.* when taken with Lie *et al.* is withdrawn in view of Applicants' arguments. In particular, the cited art does not describe large DNA vectors that have homology arms that are greater than 20 kb which is required by the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt
Thaian N. Ton
Patent Examiner
Group 1632

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER